

# Genetic Factors and the Directionality of Comorbid Disorders

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# Getting to the root(s)

"The active ingredient in Roundup moves through the weed to kill the root."



# Phenotyping SUD

Arbitrary phenotypes—ICD-m, DSM-n

Dx of substance dependence:  
≥3 out of nine symptoms  
→ 466 combinations

$$\sum \frac{n!}{k_i!(n-k_i)!}$$

Staging—opportunistic

Mixed effects: stimulants &  
depressants

And a little bit of this'd get you up  
And a little bit of that'd get you down

Mark Knopfler “*Junkie Doll*”

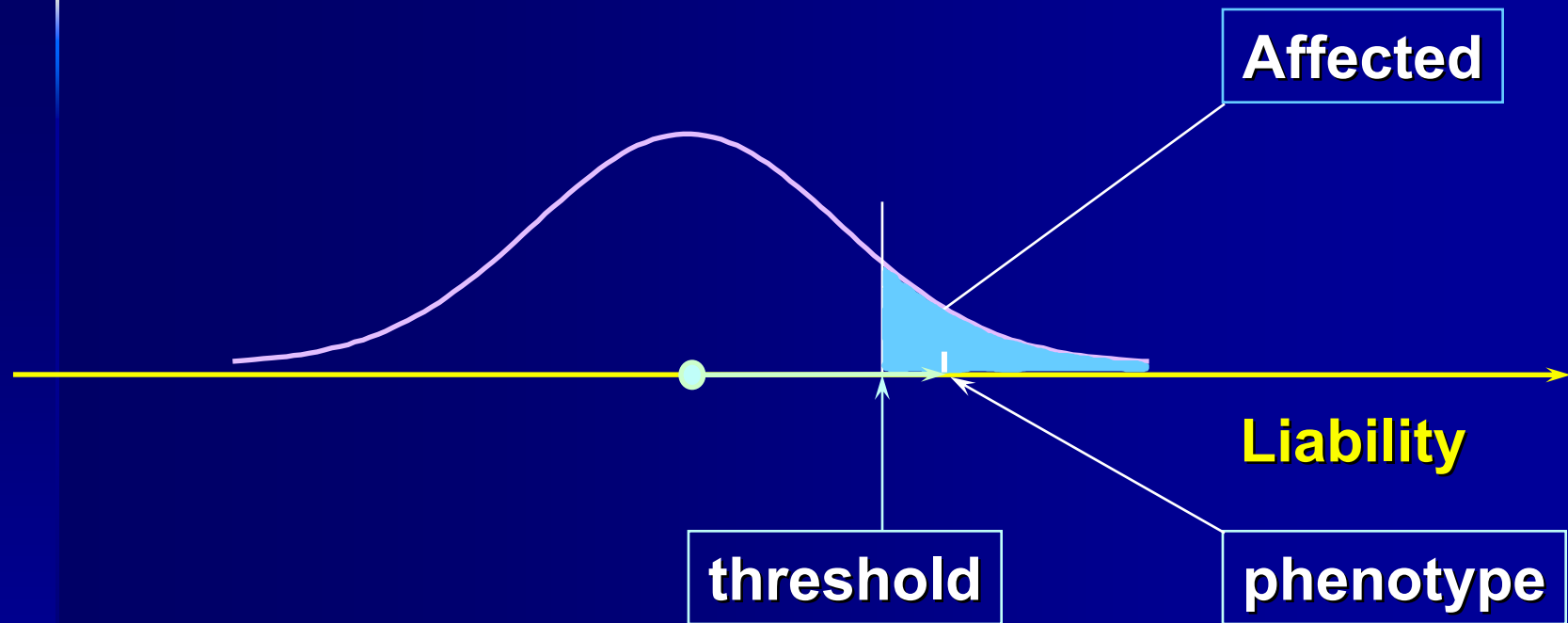


# Liability, the concept

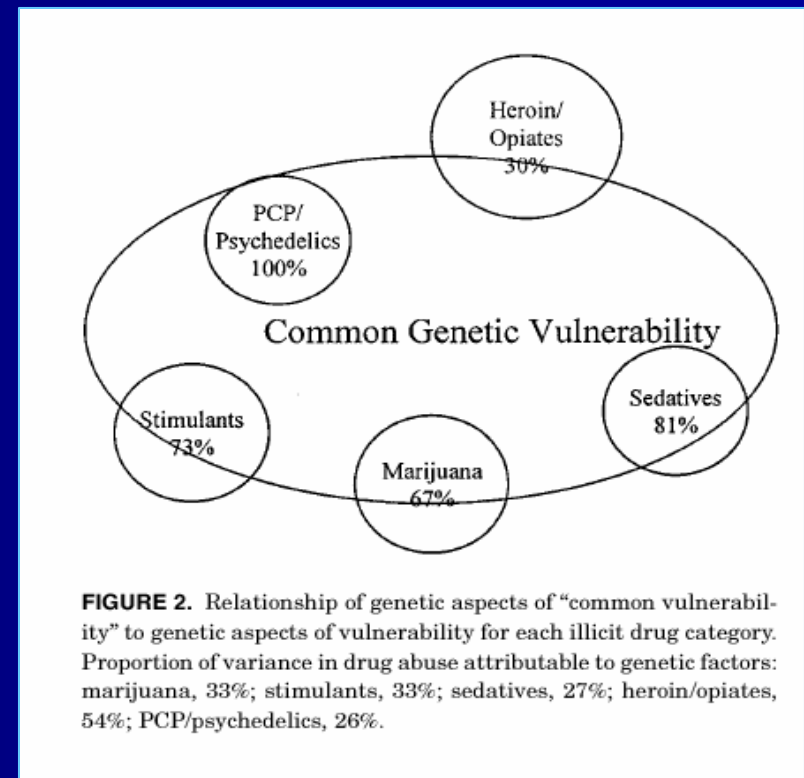
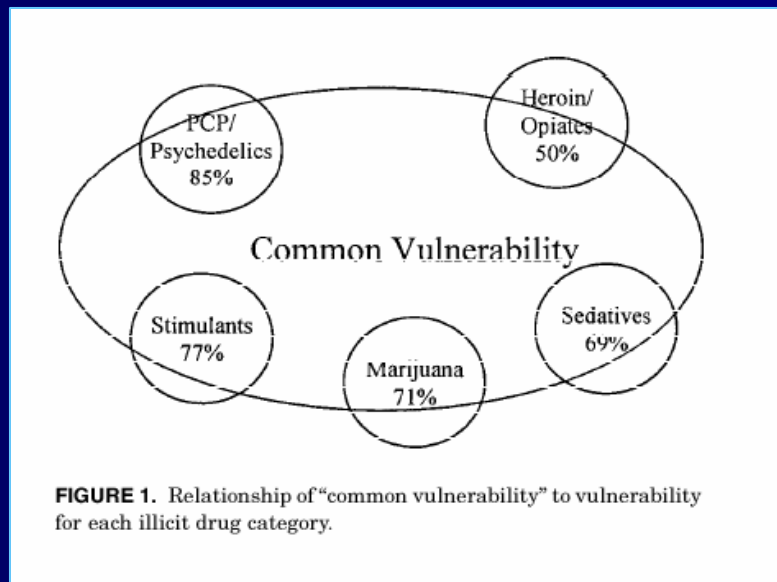
*“...to express not only the individual innate tendency to develop or contract the disease, i.e., his susceptibility in the usual sense, but also the whole combination of external circumstances that make him more or less likely to develop the disease...”*

Falconer (1965)

# Liability distribution

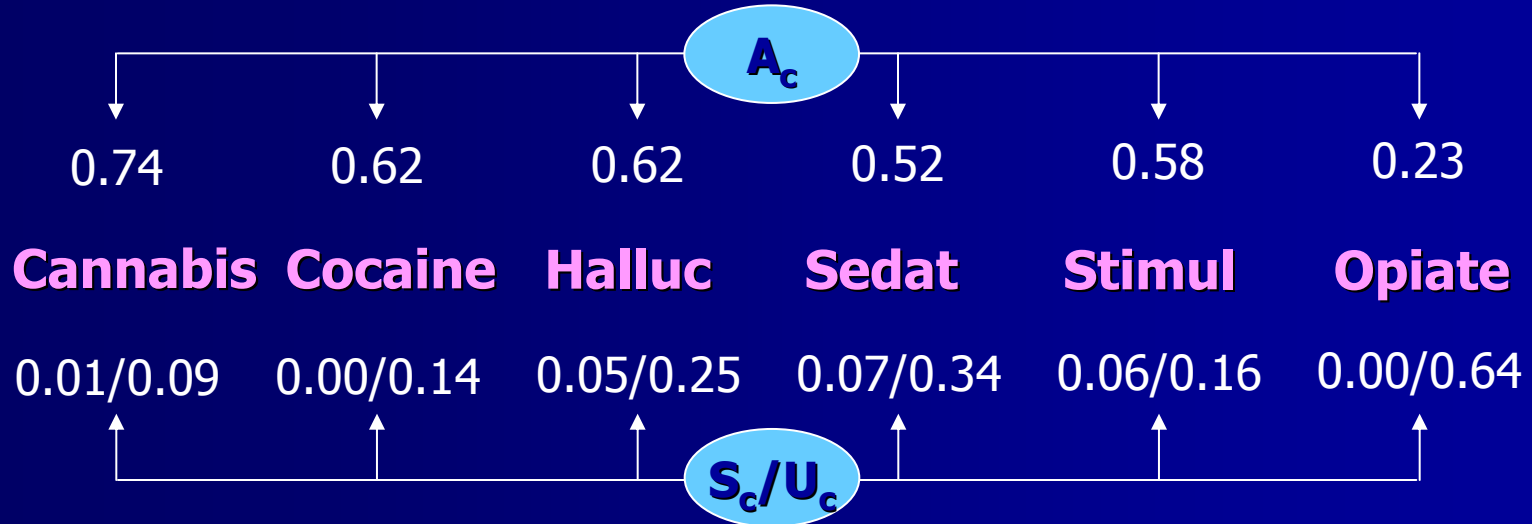


# Shared liability variance



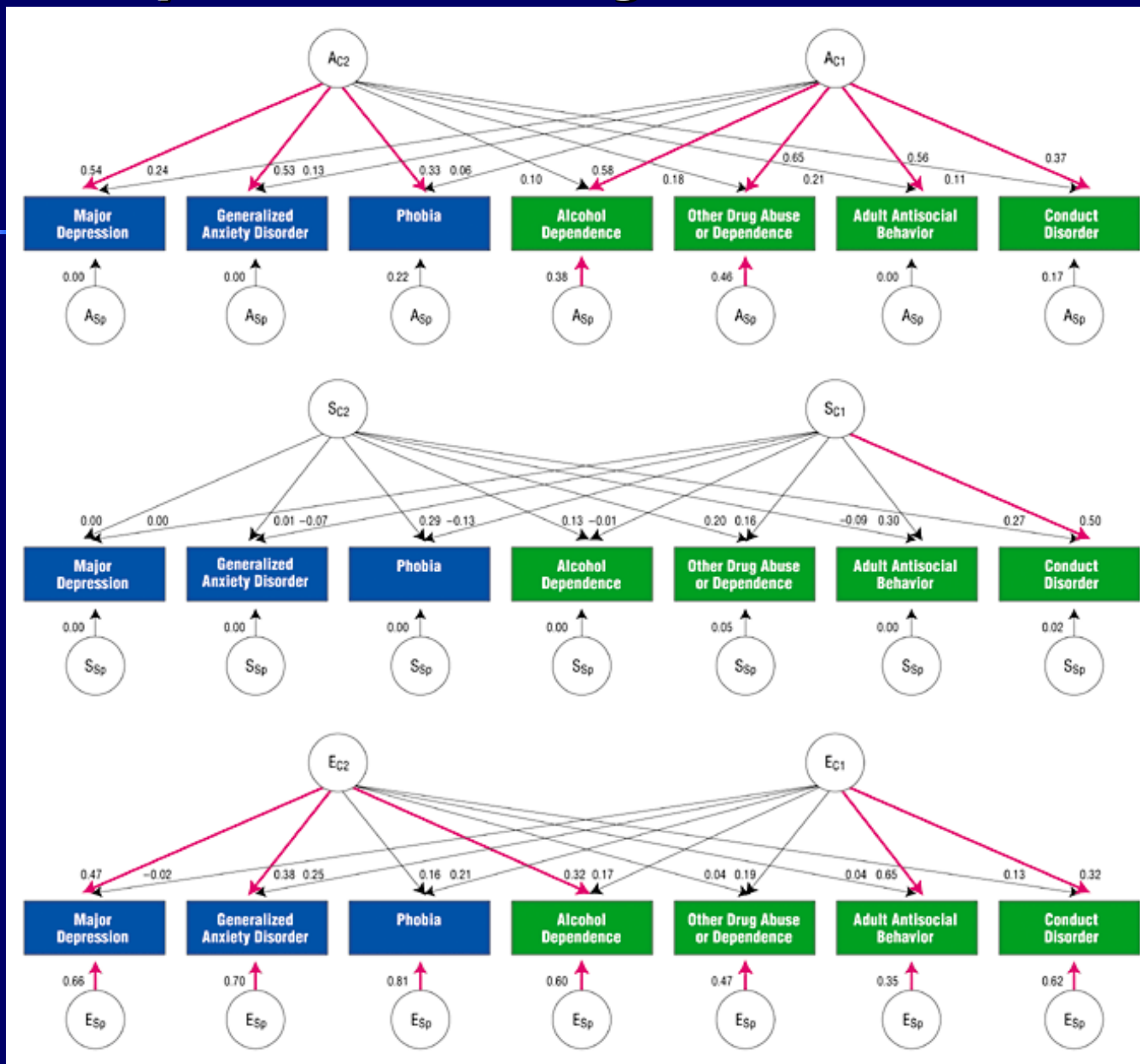
Tsuang et al., *Harvard Rev Psychiatry*, 9: 267-279, 2001

# More sharing



Kendler et al., Am J Psychiatry 160: 687–695, 2003

# Psychiatric and drug abuse disorders



Kendler, K. S. et al. Arch Gen Psychiatry 2003;60:929-937.



# Common sources of variation

## Pre-use

- Temperament
- Personality
- Cognition
- Behavior
- Self-medication

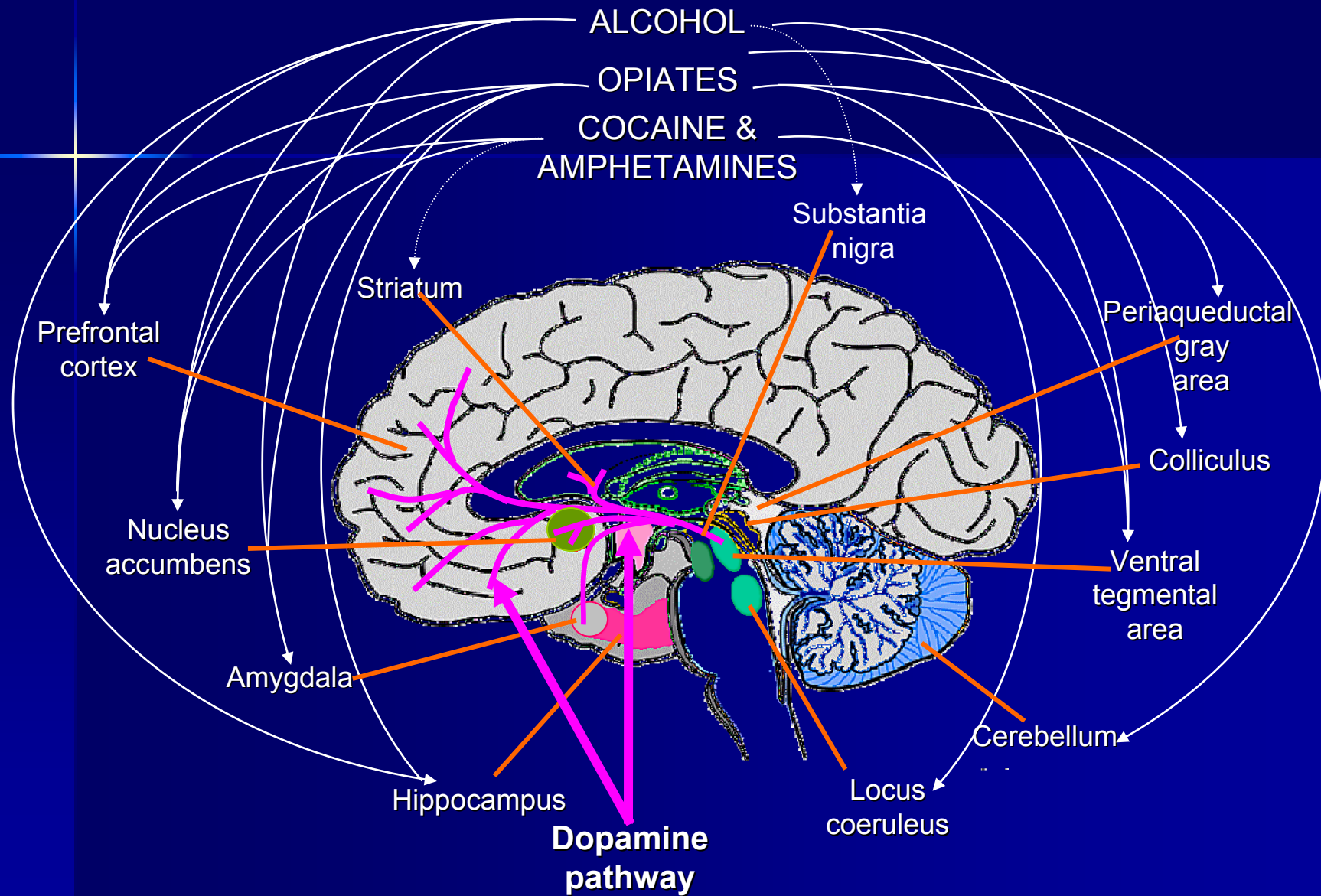
## Post-use

- Positive reinforcement
- Negative reinforcement

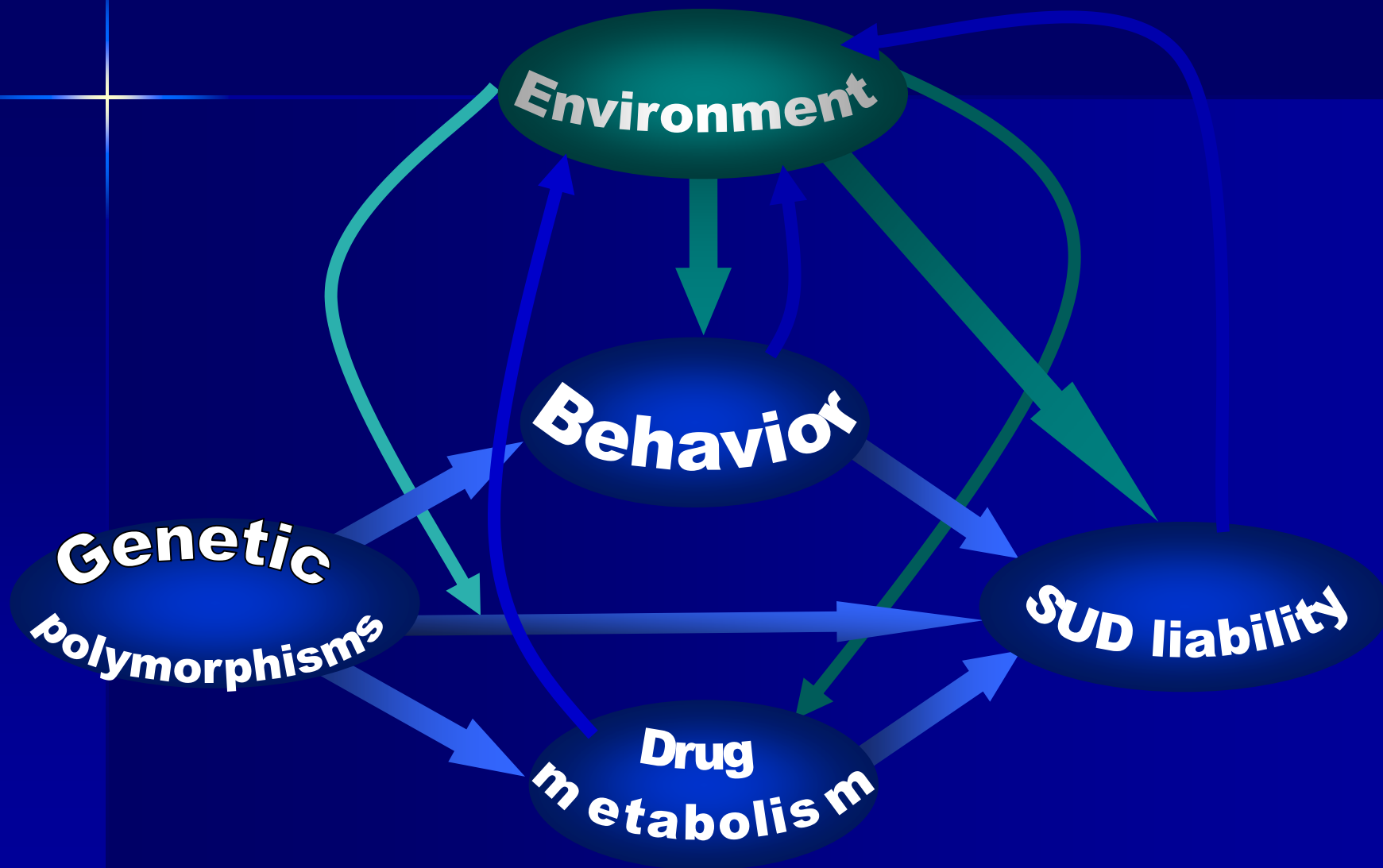


**Biobehavioral self-regulation**

# The drug-activated mesocorticolimbic dopamine pathway



# Sources of SUD risk variation

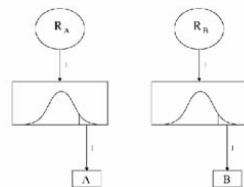


# Comorbidity models

- Chance, bias, stratification
- Alternate forms (single liability)
- Multiformity (having one increases probability of another, threshold-dependent)
- Three independent
- Correlated liabilities (threshold-independent)
  - correlated
  - one causes another
  - reciprocal causation

# Subsample of models

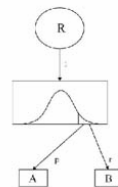
Chance



Possible Pathways for the Diagnosis of A only, B only, and AB

A only	above threshold on $R_A$ and below threshold on $R_B$
B only	below threshold on $R_A$ and above threshold on $R_B$
AB	above threshold on $R_A$ and $R_B$

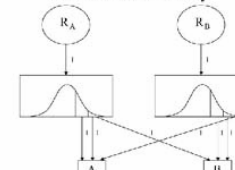
Alternate Forms



Possible Pathways for the Diagnosis of A only, B only, and AB

A only	above threshold on $R$
B only	above threshold on $R$
AB	above threshold on $R$

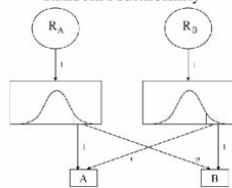
Extreme Multifactority



Possible Pathways for the Diagnosis of A only, B only, and AB

A only	above threshold on $R_A$ and below threshold on $R_B$
B only	below threshold on $R_A$ and above threshold on $R_B$
AB	1. above threshold on $R_A$ and $R_B$ 2. above threshold on $R_A$ and below threshold on $R_B$ 3. below threshold on $R_A$ and above threshold on $R_B$

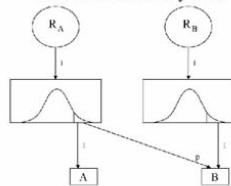
Random Multifactority



Possible Pathways for the Diagnosis of A only, B only, and AB

A only	above threshold on $R_A$ and below threshold on $R_B$
B only	below threshold on $R_A$ and above threshold on $R_B$
AB	1. above threshold on $R_A$ and $R_B$ 2. above threshold on $R_A$ and below threshold on $R_B$ 3. below threshold on $R_A$ and above threshold on $R_B$

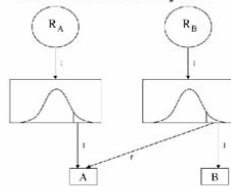
Random Multifactority of A



Possible Pathways for the Diagnosis of A only, B only, and AB

A only	above threshold on $R_A$ and below threshold on $R_B$
B only	below threshold on $R_A$ and above threshold on $R_B$
AB	1. above threshold on $R_A$ and $R_B$ 2. above threshold on $R_A$ and below threshold on $R_B$

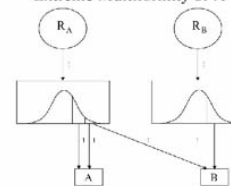
Random Multifactority of B



Possible Pathways for the Diagnosis of A only, B only, and AB

A only	above threshold on $R_A$ and below threshold on $R_B$
B only	below threshold on $R_A$ and above threshold on $R_B$
AB	1. above threshold on $R_A$ and $R_B$ 2. below threshold on $R_A$ and above threshold on $R_B$

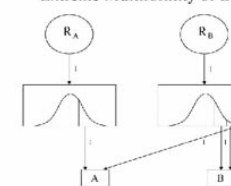
Extreme Multifactority of A



Possible Pathways for the Diagnosis of A only, B only, and AB

A only	above threshold on $R_A$ and below threshold on $R_B$
B only	below threshold on $R_A$ and above threshold on $R_B$
AB	1. above threshold on $R_A$ and $R_B$ 2. above threshold on $R_A$ and below threshold on $R_B$

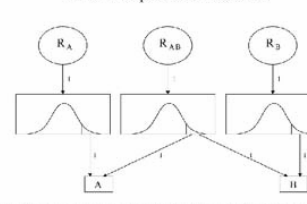
Extreme Multifactority of B



Possible Pathways for the Diagnosis of A only, B only, and AB

A only	above threshold on $R_A$ and below threshold on $R_B$
B only	below threshold on $R_A$ and above threshold on $R_B$
AB	1. above threshold on $R_A$ and $R_B$ 2. below threshold on $R_A$ and above threshold on $R_B$

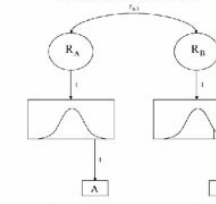
Three Independent Disorders



Possible Pathways for the Diagnosis of A only, B only, and AB

A only	above threshold on $R_A$ and below threshold on $R_{AB}$
B only	below threshold on $R_{AB}$ and above threshold on $R_B$
AB	1. above threshold on $R_A$ and $R_B$ 2. above threshold on $R_{AB}$

Correlated Liabilities



Possible Pathways for the Diagnosis of A only, B only, and AB

A only	above threshold on $R_A$ and below threshold on $R_B$
B only	below threshold on $R_A$ and above threshold on $R_B$
AB	above threshold on $R_A$ and $R_B$

# Genetics in SUD risk

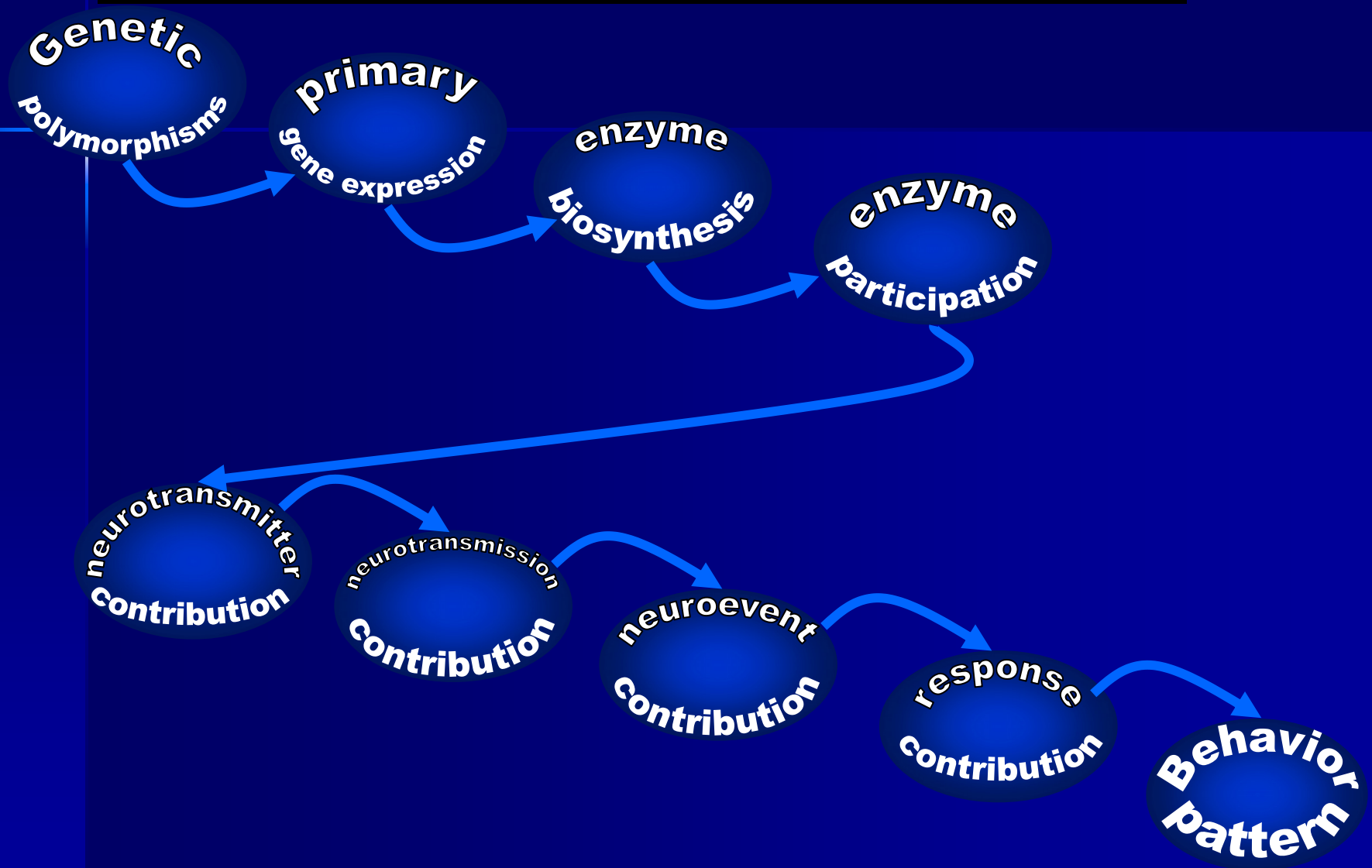
**Genes**

in determination  
in variation

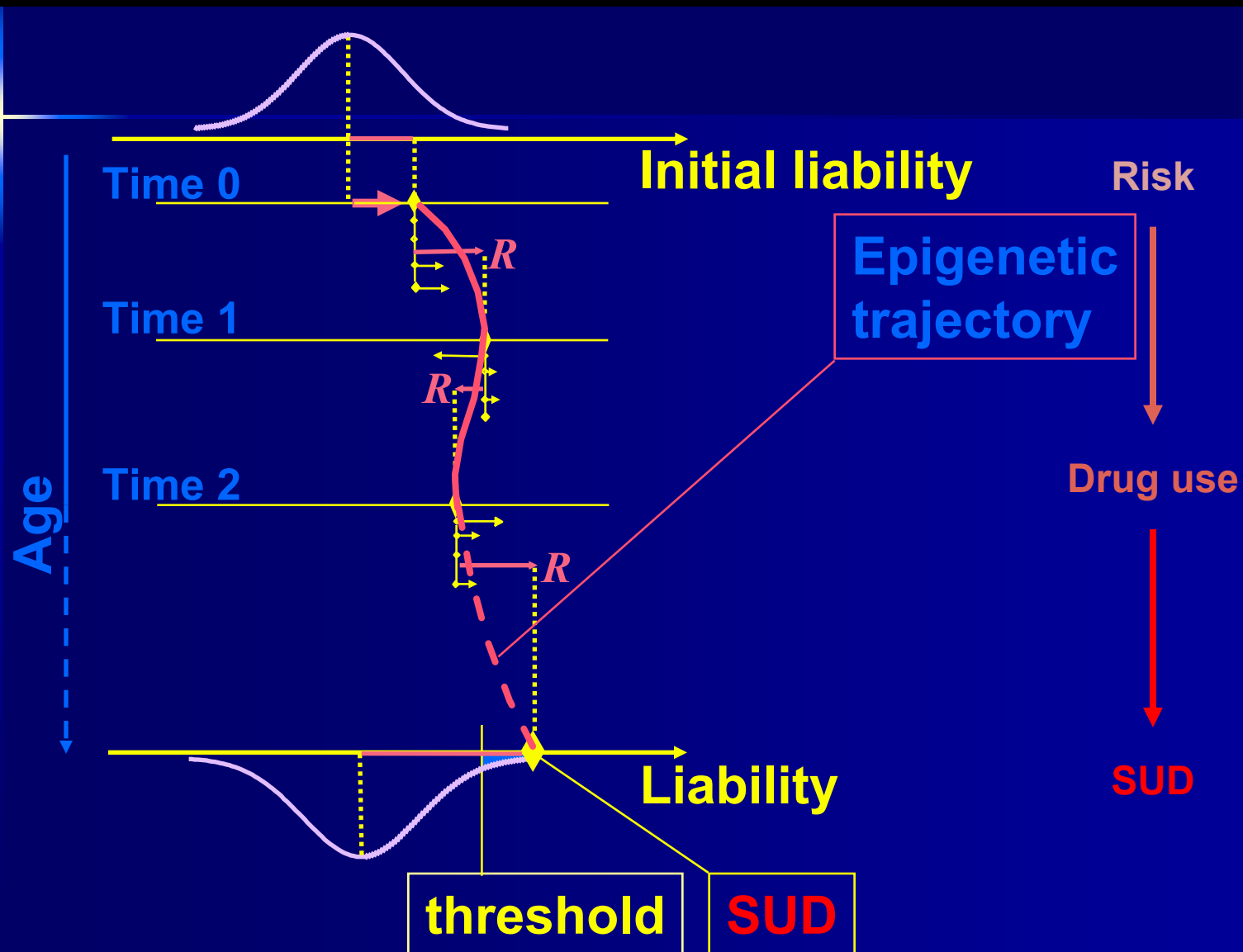
**SUD liability**



# It's a long way ...



# Dynamic liability: Tracking etiology and comorbidity of SUD





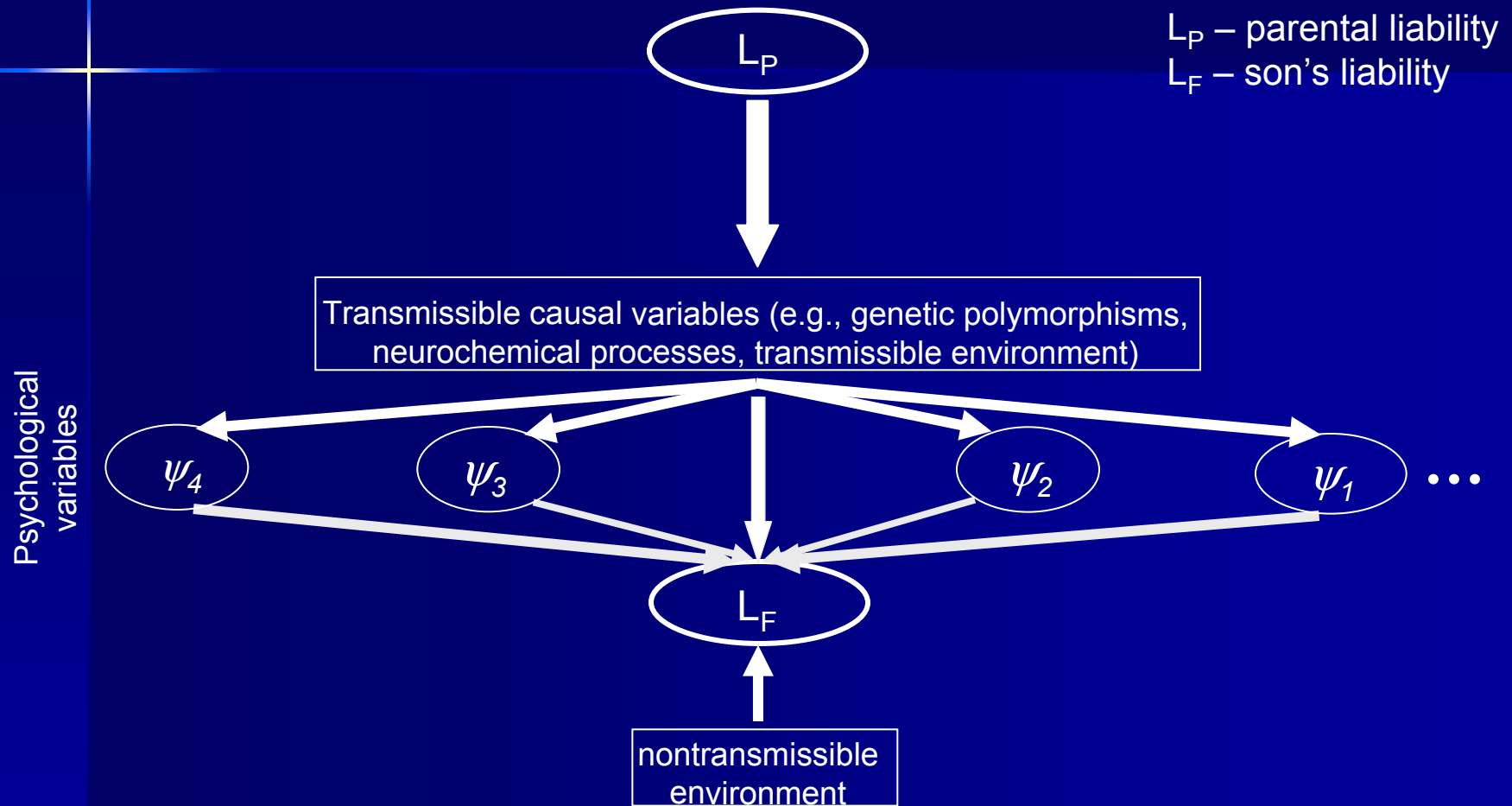
# Genetics & comorbidity

- Behavior genetics
  - genetic and environmental correlations
  - developmental tracking
- Molecular genetics
  - association/linkage
  - mediation by intermediate traits
- “Hybrids”

# Family history

- Faster physiological maturation
- Detachment from parents
- Homophilic peer selection/contagion
- Dysregulation/disinhibition
- Maladjustment
- SU/SUD

# Determination of SUD liability



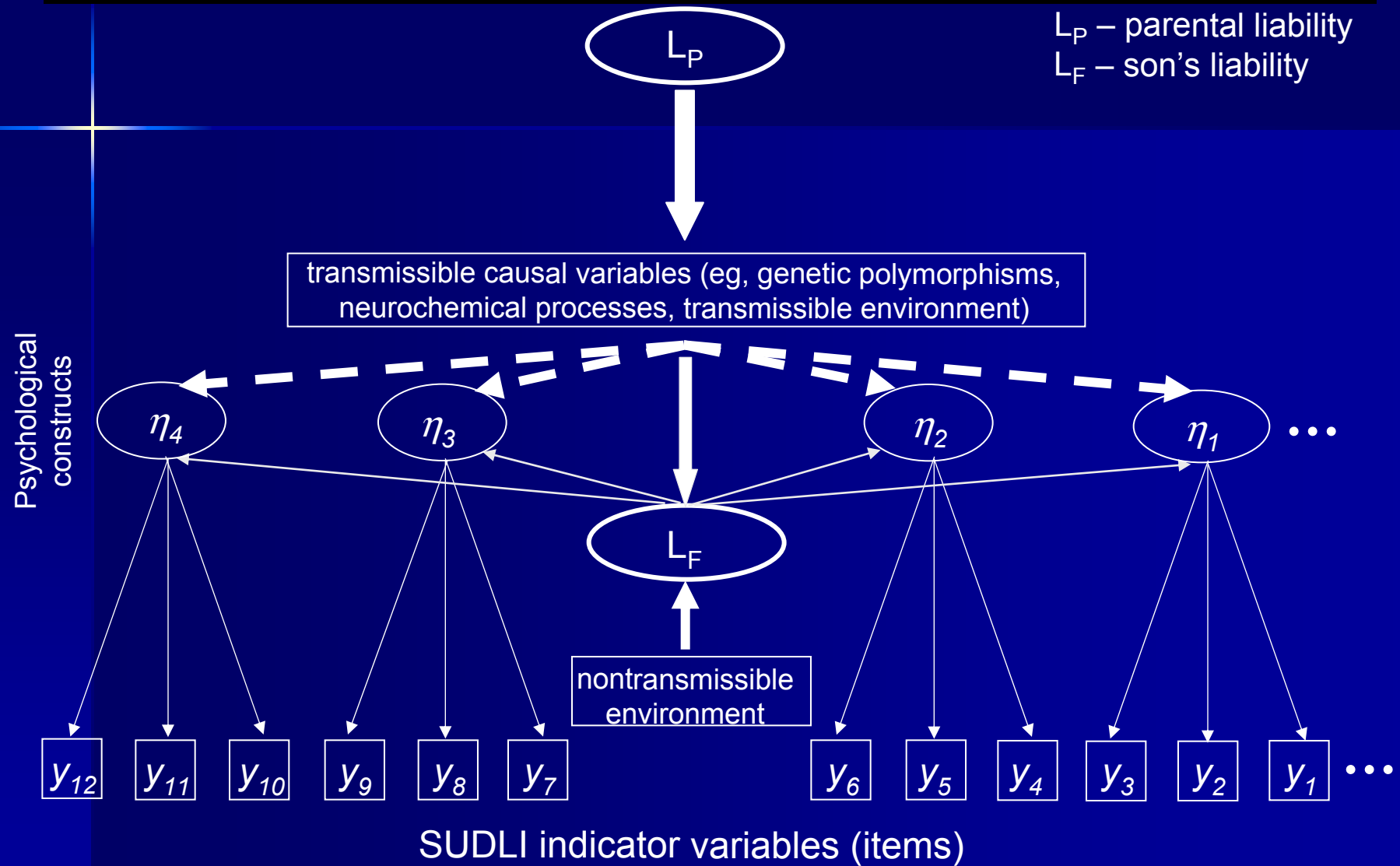
# DBD and the rate of SUD

<u>Diagnosis</u>	<u>HR</u>	<u>95% CI</u>	<u>P</u>
ADHD	2.81	1.42-5.55	0.003
CD	7.17	2.78-18.52	0.00005
ODD	2.20	1.04-4.63	0.038

dysregulation

# Measurement of SUD liability

$L_P$  – parental liability  
 $L_F$  – son's liability



# DRD4-ERP-Disinhibition

- Family-based analysis (FBAT)
- Promoter region (-521) SNP
- ERP—ND:  $p=.02$
- SNP—>P300:  $p=.004$
- SNP—>ND:  $p=.003$
- SNP—>ND|P300:  $p=.85$

# Parenting & MAOA

Dependent	Sample	Predictor	Hazard ratio (95% CI)	P
CD	full	dad	0.504 (0.289-0.879)	.016
		mom×dad	0.652 (0.456-0.932)	.019
	4R	dad	0.380 (0.179-0.805)	.011
		mom	1.601 (0.989-2.591)	.055
	3R	dad	0.796 (0.343-1.850)	.597
		mom	1.099 (0.534-2.265)	.797
ADHD	full	mom×dad	1.558 (1.031-2.353)	.035
		dad×MAO	3.299 (1.479-7.356)	.004
	4R	dad	1.974 (1.230-3.168)	.005
		mom×dad	1.799 (1.057-3.062)	.030
	3R	dad	0.574 (0.256-1.284)	.177
		mom×dad	1.604 (0.719-3.578)	.249
SUD	full	MAO	0.382 (0.155-0.940)	.036

Vanyukov et al. (in press) Psychiatric Genetics

# MAOA & SUD

## Low activity

- increase in the risk
- limbic volume reductions, hyperresponsive amygdala during emotional arousal, diminished reactivity of regulatory prefrontal regions (Meyer-Lindenberg et al., 2006)



# Drug use severity

Trait

Drug Use Screening Inventory  
substance use problems scale

Sample

94 male Caucasian adolescents  
(12-18 years of age) with a  
DSM-IV diagnosis of Substance  
Dependence related to illicit  
drugs

Genes

Polymorphisms in DRD1-DRD5  
genes

Analysis

Two-way ANOVA, testing main  
effects and interactions  
between D1- and D2-family  
genes

# Interactions as expected

<i>Predictor sets</i>	<i>df</i>	<i>F</i>	<i>p</i>
DRD1.1	2	2.28	.108
DRD2	1	0.02	.898
DRD1.1×DRD2	1	4.39	.039
DRD1.1	2	3.63	.031
DRD3	4	1.09	.369
DRD1.1×DRD3	6	2.29	.044
DRD1.7	2	4.47	.015
DRD3	4	0.72	.584
DRD1.7×DRD3	6	2.60	.025

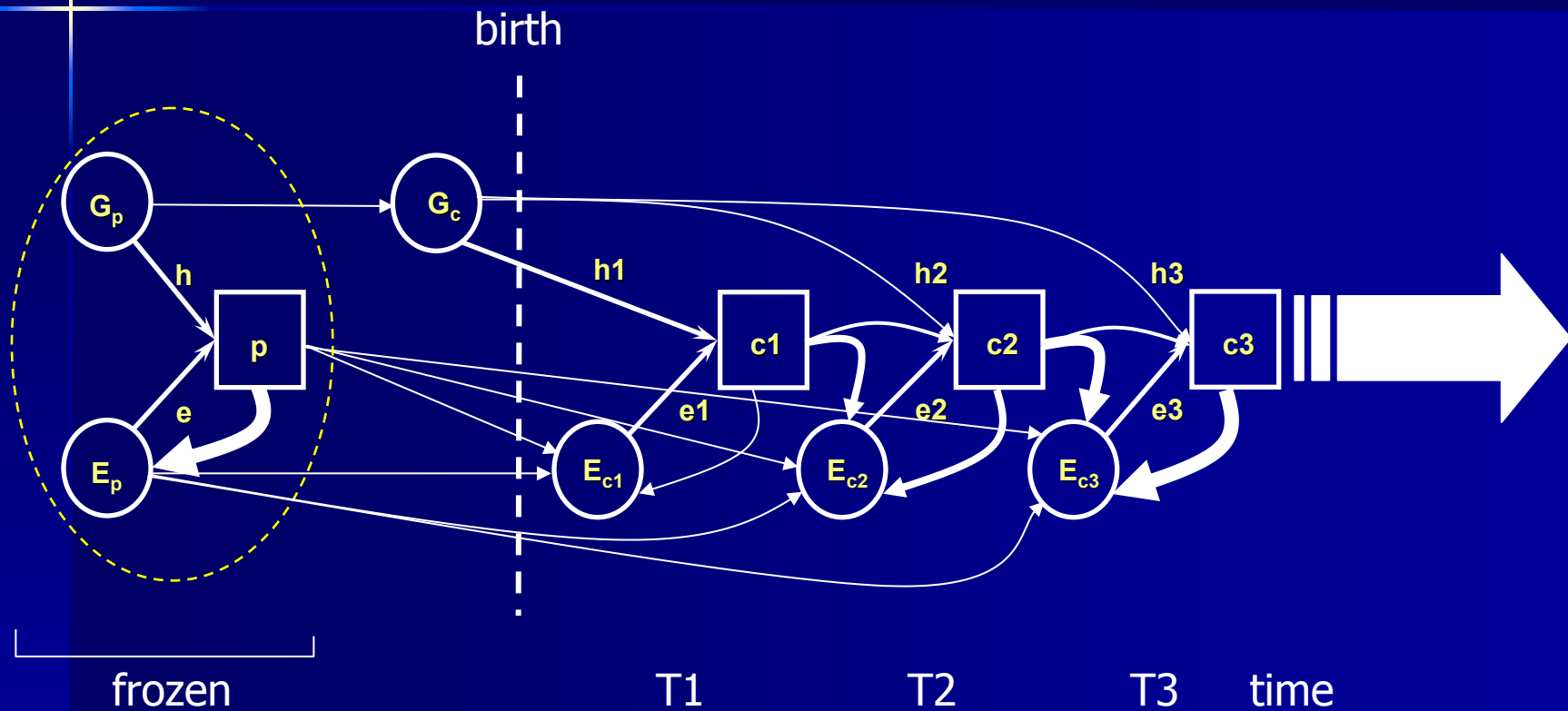
# Candidate system genes

*Comorbidity helps:*

multiple hits

- cross-verify
- identify pathways
- support the gene's role

# Dynamic



Note:  $G \times E$  omitted

# Genetic roots

... environmental "Roundup"?

